

# Current and lifetime psychiatric illness in women with Turner syndrome

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## ABSTRACT

*Abnormalities in quality of life and cognitive measures have been observed in women with Turner syndrome (TS), and a relationship between these phenomena and chromosomal constitution has been suggested. In contrast, few studies have systematically evaluated the presence of mood and behavioral syndromes in these women. In this study, 100 TS women were administered the Structured Clinical Interview for DSM IV after a two-week period during which their hormone replacement had been discontinued. The majority of women who met criteria for a psychiatric condition had a mood or anxiety disorder. Overall, 52 (52%) of the TS women met criteria for a current or a past depressive or anxiety disorder. Eighteen of the women with TS met criteria for a current Axis I psychiatric disorder [Depression – major (n = 5), minor (n = 5), dysthymia (n = 1); Anxiety (n = 9)]. Forty-six of the women with TS met criteria for a past Axis I psychiatric illness [Depression: unipolar (n = 41), bipolar (n = 3); Anxiety (n = 7); eating disorder (n = 6); substance dependence (n = 3)]. Five women with TS met criteria for an Axis II personality disorder. Women with TS reported a higher rate of lifetime depression compared with rates observed in community-based studies*

*but similar to those obtained from gynecologic clinic samples.*

## INTRODUCTION

The loss of all or part of the 2nd X sex chromosome during embryogenesis results in Turner syndrome (TS), or monosomy X. This relatively common chromosomal disorder affects ~1/2500 live female births, with short stature and hypogonadism the most common clinical findings<sup>1–3</sup>. Anatomical features such as lymphedema, skeletal abnormalities and congenital heart and kidney defects are found in about 50% of affected individuals<sup>1,2</sup>. Brain development also may be affected in TS, with several neuroimaging studies reporting anatomical and functional differences between girls or women with TS and age-matched controls in the parietal and dorsolateral prefrontal cortices, superior temporal gyrus, hippocampal formation, amygdala, and temporal lobes<sup>4–8</sup>. Supporting the possibility of brain involvement, girls and women with TS

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demonstrate a distinct neurocognitive profile where verbal ability is generally normal<sup>9–11</sup> while visual-spatial abilities, working memory and executive function may be impaired<sup>12–15</sup>.

While specific cognitive deficits have been documented in TS, the prevalence of psychopathology in this disorder has only been addressed in a few small studies. There seems to be a consensus that many girls with TS exhibit immaturity, poor self-esteem and difficulties with social relationships, and appear more likely to receive diagnoses of non-verbal learning disorder and/or ADHD<sup>16,17</sup>. Skuse and co-workers have suggested that individuals with TS have difficulty in reading facial expressions connoting emotions, especially fear (as seen in autism)<sup>18</sup>, as well as social problems, and have related these behavioral traits to both an amygdalar dysfunction and a maternal origin of the single normal X-chromosome<sup>18–21</sup>. Whether these psychological features observed in girls with TS portend an increased risk of psychiatric diagnoses in adult life is unclear. The few prior studies<sup>16,22,23</sup> showed a broad range of lifetime prevalences of psychiatric disorders in TS women.

In the present study we have employed structured diagnostic interviews to establish the prevalence of DSM-IV diagnoses in a large population of women with TS from across the United States.

## METHODS

### Subjects

Women with TS provided written informed consent/assent for voluntary participation in this study protocol approved by the National Institute of Child Health and Human Development (NICHD) Institutional Review Board. This psychiatric evaluation was one component of a primary protocol that involves a 4–5 day stay in the NIH Clinical Research Center. All study subjects were phenotypic females, at least 16 years of age, with a diagnosis of TS that was confirmed by a 50-cell peripheral karyotype in which > 70% of cells demonstrated loss of all or part of the 2nd sex chromosome. Study subjects discontinued the use of ovarian hormone or growth hormone treatment two weeks prior to admission (for reasons related to the primary protocol) and were euthyroid and in good general health based on laboratory and clinical evaluations. Study subjects were recruited primarily

through notices on the web and the NIH home page.

From an initial sample of 112 TS women, nine were excluded on the grounds of being less than 16 years of age, and three adults declined participation. One hundred TS women were evaluated with the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (fourth edition) (SCID I & II)<sup>24</sup>, a structured diagnostic interview that establishes the presence or absence of Axis I and II diagnoses. SCID interviews were administered by GC, RD, NH, and PS.

The number of women with TS meeting criteria for an Axis I disorder were tabulated. The percentages of women with TS who met SCID criteria for current and lifetime (defined as the occurrence of an Axis I disorder at any time in the woman's life) mood and anxiety disorders were compared with published prevalence rates of these disorders from several large community-based studies<sup>25–27</sup> and gynecologic clinic-based samples<sup>28</sup>. Additionally, in those women with and without a lifetime affective disorder we examined possible differences in the number of women who either received hormonal therapies (thyroid and GH) or had physical stigmata of TS (i.e., webbing of the neck or short stature) by Chi square and Student's *t* test (height only). Finally, we compared the number of women meeting criteria for a lifetime psychiatric disorder in the women with TS with a 45-X genotype and other genotypes (see below) by Chi square.

## RESULTS

### Subject characteristics

The mean age of our study group was  $34.7 \pm 11.6$  years with a range of 16–61 years (Table 1). The great majority (91%) were Caucasian with the remainder consisting of African American, Hispanic and Asian women; 62% had never married and only three had children. The group as a whole was highly functional, with women greater than 22 years old having an average of  $16.3 \pm 2.1$  years of formal education, while the younger women were generally in high school or college. Forty women (40.4%) had webbing of the neck, 32.7% had a history of past or current treatment with growth hormone (GH), 33% were currently on thyroid hormone replacement, and all women received

**Table 1** Characteristics of women with Turner syndrome ( $n = 100$ ), mean (SD)

	<i>Turner syndrome (TS)</i>
Age yrs [range]	34.7 (11.6) [16–61]
Marital status (% single)	62
Caucasian (%)	91
Height (cm)	146.2 (10.0)
BMI	27.6 (6.5)
Education (yrs)	15.5 (2.7)
No. on BCP/HRT	56/40*
Duration of HRT (yrs)	14.6 (10.7)
No. on GH	32**
No. on thyroid H	33
No. on antidepressants	14
No. with webbing of neck	40§
Free testosterone	6.8 (4.3) pg/ml
No. with children	9 (3 biological, 6 adopted)

\*data missing in four women

\*\*data missing in two women

§data missing in one woman

some form of HRT (oral contraceptives (58%), the remaining were on estrogen and progestin therapy). The women received hormone replacement therapy for an average of  $14.6 \pm 10.7$  years. Fourteen women were currently taking antidepressants. The karyotype distribution for the 100 women in this study was approximately: 67% 45,X; 19% 45,X/46,XX or 46,XY (< 30% normal cells); 10% 46,XiXq or 46,XiXq/45,X with < 10% 45,X; 4% 46,XdelXp or 45X/46,XdelXp with a few 45,X/46,XrX, (ring X condition) all with retained X inactivation segments.

### Psychiatric diagnosis

Forty-eight percent of women did not meet criteria for any current or past Axis I psychiatric diagnosis, and only five women met criteria for an Axis II (personality) disorder (three of whom also met criteria for an Axis I condition). Eighteen percent of women with TS met criteria for a *current* Axis I diagnosis: 11% affective disorders (mainly major depression (5%), minor depression (5%) and dysthymia (1%)), and 11% anxiety disorders. Depressive and anxiety disorders coexisted in four women. Comparable rates of *current* Axis I diagnoses from community-based and gynecology clinic-based samples of women are listed in Table 2.

**Table 2** Axis I and II diagnoses in women with Turner syndrome ( $n = 100$ )

	<i>Current psychiatric diagnosis (n = 18)</i>	<i>Past psychiatry diagnosis (n = 46)†</i>
Affective disorders	<b>11</b> (7%)*	<b>44</b>
Major depression	5 (3–6%) [6%]	33
Minor depression	5	8
Dysthymia	1	0
Bipolar disorder	0	3
Anxiety disorders	<b>11</b> (10%)	<b>[7%] 7</b>
Panic disorder	4	1
Social phobia	2 (1–4%)	0
Generalized anxiety disorder	2	0
Specific phobia	2	1
Anxiety disorder NOS	1	0
PTSD	0	5
Eating disorder	<b>0</b>	<b>6</b>
Anorexia	0	5
Bulimia	0	1
Substance dependence	<b>0</b>	<b>3</b>
Axis II diagnosis	<b>5</b>	
Avoidant	2	
Borderline	1	
Obsessive	2	

\*Published rates of current Axis I diagnosis appear in rounded parentheses ( ) from community samples<sup>25–27</sup> and in square parentheses [ ] from gynecology clinic samples<sup>28</sup>

†46% of women with TS did not meet SCID criteria for current or past Axis I or II psychiatric diagnosis

A *past* Axis I diagnosis was observed in 46% of women with TS and reflected a predominance of affective disorders (44%), with 33% of women meeting criteria for a past major depression. A past history of both affective and anxiety disorders was present in three women, affective and eating disorders in five women, and two women had two or more Axis I diagnoses.

Lifetime major depression occurred in 36% of women, and lifetime affective disorders (any mood disorder) in 47% of women, compared with rates in the community of 21% and 24%, respectively<sup>27</sup> (as well as 63% [lifetime affective disorders] in one gynecology clinic-based study<sup>29</sup>). Lifetime histories of anxiety disorders were observed in 15% of women with TS and in 15–30% of women in community studies.

Comparison between TS women with and without lifetime affective disorders showed no differences in the presence of webbing of the neck (Chi-square = 0.08,  $p = \text{NS}$ ), history of treatment with GH (Chi-square = 0.9,  $p = \text{NS}$ ), and current treatment with thyroid hormone (Chi-square = 0.9,  $p = \text{NS}$ ). Additionally, height did not significantly differ in those women with and without an affective disorder (Students  $t_{99} = 0.2$ ,  $p = \text{NS}$ ).

## DISCUSSION

This study represents the largest case series focusing on the psychiatric status of women with TS. Our major finding was that women with TS do not report substantially higher rates of current psychiatric disorders including depression or anxiety disorders, compared to published community-based prevalence rates. A higher lifetime rate of mood disorders (but not psychiatric disorders in general) was observed in women with TS compared to that reported in community-based samples, but comparable to that observed in gynecology clinic-based samples.

Recently there has been considerable attention focused on improving the quality of life in women with TS. Enhanced social and family support networks and treatment with growth hormone and estrogen with or without androgen replacement therapies early in the course of TS may contribute to an improved quality of life. However, the presence and impact of co-existing psychiatric morbidity has received little attention. Indeed, neuro-imaging studies in women with TS have identified abnormalities in several brain regions relative to controls including the dorsolateral prefrontal cortex, amygdala, and hippocampus<sup>4,7,30–33</sup>. The function of these brain regions also has been reported to be altered in mood disorders<sup>34,35</sup>, and, therefore, the neuroimaging data would suggest that women with TS may have an increased risk for the development of affective disorders. In this study, the number of women with TS who met criteria for a current Axis I psychiatric illness was comparable to reported rates of women in several community-based<sup>25–27</sup> and gynecology clinic-based<sup>28,29</sup> samples. Specifically, rates of current mood and anxiety disorders were not substantially increased in women with TS despite discontinuing hormone replacement therapy for the two weeks prior to the interview. The rate of *lifetime* psychiatric diagnoses was almost twice as high in women with TS compared to commu-

nity-based samples and reflected a higher rate of mood but not anxiety disorders in these women. However, both the current and lifetime rates of mood disorders were not substantially higher than those previously reported in either medical outpatient<sup>36,37</sup> or gynecology clinics<sup>29</sup>. Thus, our data would suggest that TS is not associated with an increased risk of depressive illness, beyond that expected to occur in association with any medical or gynecologic condition.

Three previous studies have evaluated the presence of psychiatric diagnoses in women with TS. Delooz et al.<sup>22</sup> administered a structured diagnostic interview to 20 women with TS and observed rates of lifetime psychiatric illness of 50% (the majority of which were mood disorders) and current mood disorders of 20%. Albeit in a substantially smaller sample, the data of Delooz et al. are comparable to our findings. In contrast two other studies reported lower and higher rates of psychiatric illness, respectively. McCauley et al. observed a 22% lifetime prevalence of psychiatric illness in a sample of 27 women with TS<sup>38</sup>. The small sample size and the absence of a structured diagnostic interview may account for the discrepant findings of this study. In contrast, Downey et al. administered a structured diagnostic interview to 23 women with TS drawn from their private practice and reported a 70% lifetime prevalence of psychiatric illness<sup>23</sup>. However, the higher rate of lifetime psychiatric illness observed by Downey et al. may reflect the selection of women with more severe mood and behavioral symptoms present in this practice.

Abnormalities of thyroid function<sup>39</sup> and growth hormone secretion<sup>40</sup> both are associated with the appearance of mood disorders; however, in our sample there was no increased number of women treated with either hormone in the women meeting criteria for a past or current affective disorder compared to those with no history of psychiatric illness. Similarly, despite possible associations between mood symptoms and the physical stigmata of TS, the presence of a webbing of the neck<sup>41,42</sup> or short stature<sup>43,44</sup> was not disproportionately represented in the women with mood disorders. Finally, our data did not suggest a difference in the risks for psychiatric disorders in those TS women with 45X compared to those with other karyotype abnormalities, including mosaic patterns.

Several observations in women with TS also suggest that they experience distressing social

anxiety<sup>45</sup>. First, clinical reports have documented that women with TS experience more social anxiety and shyness than matched controls<sup>46</sup>, traits proposed to be on a continuum with some anxiety disorders such as social phobia<sup>47,48</sup>. Second, women with TS have been observed to display deficits in several social processes including difficulty recognizing facial expressions and determining the direction of eye gaze. Finally, both structural and functional neuroimaging studies have identified alterations in several brain regions associated with social cognition and behavior<sup>32,49,50</sup> in women with TS compared to controls including the amygdala, superior temporal sulcus, and orbitofrontal cortex<sup>20</sup>. We observed only two women out of the 100 interviewed who met criteria for social phobia, and only four additional women met criteria for panic disorder. Thus our data do not suggest that the social difficulties reported by many women with TS lead to the syndrome of social phobia or other anxiety disorders. Moreover, it is remarkable that so few women with TS met criteria for social phobia given prior reports of the high rate of shyness and social anxiety present in women with TS<sup>46</sup>. Our data, therefore, would suggest that in the context of a medical condition like TS, the excessive shyness and social anxiety does not progress to a clinical syndrome of social phobia in the vast majority of women.

Several case reports suggested a higher than expected prevalence of eating disorders in TS<sup>51,52</sup>. In fact, the association between these two conditions was interpreted by some to reflect a common pathophysiology, whereas others suggested the co-occurrence of these conditions is predicted by their prevalence rates and chance<sup>53,54</sup>. None of the women in this study met criteria for a current eating disorder. Although the 6% of our sample who met criteria for a past history of an eating disorder is higher than the 1% prevalence rate in the general population<sup>55</sup>, it approximates that reported in medical conditions such as diabetes mellitus (up to 8.3%)<sup>56</sup>. Thus our data would not suggest a specific relationship between TS and eating disorders other than what has been observed in the context of a general medical condition.

The present findings represent the largest sample of women with TS to be evaluated with a structured diagnostic interview. Our findings may differ from a population-based study on TS, since many of the women were self-referred, and our sample may have been a healthier, more motivated and less shy group of women. Nonetheless, the comparable rates of psychiatric conditions in this large sample of women to those published prevalence rates in gynecology clinics suggests that the neurobiologic and genetic abnormalities in TS do not uniquely or uniformly lead to psychiatric syndromes.

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